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(54) Production of 2-(2-Pyridylmethylsulfinyl)Benzimidazole Compounds

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Abstract of the disclosure

2-(2-pyridylmethylsulfinyl)benzimidazole compounds are produced by subjecting 2-(2-pyridylmethylthio)benzimidazole compounds to oxidation with hydrogen peroxide in the presence of vanadium compounds in good yield and with low production of by-products.

Production of 2-(2-Pyridylmethylsulfinyl)benzimidazole Compounds

This invention relates to the production of 2-(2-pyridylmethylsulfinyl)benzimidazole compounds (refer to, for example, U.S. Patent No.4255431, European Patent Laid-Open No.45200, No.74341, No.80602, No.5129, No.174726, No.175464, British Patent Laid-Open No.2134523A), which are useful as antiulcer agents.

As a method for production of 2-(2-pyridylmethylsulfinyl)benzimidazole compounds, an oxidation of the corresponding 2-(2-pyridylmethylthio)benzimidazole compounds with m-chloroperbenzoic acid is mentioned (refer to, for example, U.S. Patent No.4255431, European Patent Laid-Open No.80602).

Generally known methods for production of sulfoxides from sulfides include oxidation with peracid, hydrogen peroxide, iodosobenzene, N-halosuccinimide, tertiary butyl hypochloride, sodium metaperiodate, selenium dioxide, bromine, chlorine, or ozone [Refer to: Saul Patai, The chemistry of ethers, crown ethers, hydroxyl groups and their sulphur analogues, Supplement E, Part 1, p.539-608, John Willey & Sons, An Interscience Publication (1980), Michel Madesclaire, Tetrahedron Report Number 210, "Synthesis of Sulfoxides by Oxidation of Thioethers", Tetrahedron, 42, 5459-5495 (1986)].

However, the specifications or references do not include concrete examples of practical production of 2-(2-pyridylmethylsulfinyl)benzimidazole compounds by oxidation with hydrogen peroxide as the oxidizing agent.

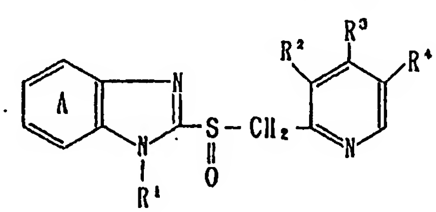
Oxidation of 2-(2-pyridylmethylthio)benzimidazole compounds with m-chloroperbenzoic acid gives 2-(2-pyridylmethylsulfinyl)benzimidazole compounds only in low yields, producing much side products such as 2-(2-pyridylmethyl-

sulfonyl)benzimidazole N-oxide. Such side products are very difficult to remove from 2-(2-pyridylmethylsulfinyl)benzimidazole compounds with usual methods of purification, such as recrystallization. Expensiveness of m-chloroperbenzoic acid is an additional problem.

There are some problems in oxidation of 2-(2-pyridylmethylthio)benzimidazole compounds with one of the oxidizing agents described above other than hydrogen peroxide; the reaction will not proceed in many cases, and the yield is very low (less than about 75%) because of degradation or production of a great ammount of by-products.

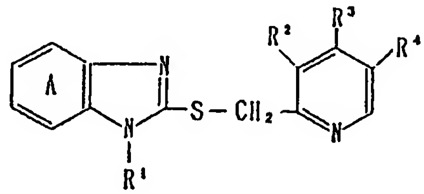
As the results of the inventors' researches to find a method for production of 2-(2-pyridylmethylsulfinyl)benzimidazole compounds from 2-(2-pyridylmethylthio)benzimidazole compounds in good yield and with low production of by-products such as 2-(2-pyridylmethylsulfonyl)benzimidazole N-oxides, the inventors have found that oxidation with hydrogen peroxide in the presence of vanadium compounds, for example, vanadium oxides or vanadium salts, as the catalyst accomplishes the purpose, and have completed the invention after further researches.

This invention relates to a method for producing a compound having the formula (II):



(II)

wherein the ring A may be substituted; R^1 is a hydrogen atom or an N-protective group; R^2, R^3 and R^4 are independently hydrogen atom, an alkyl group which may be fluorinated or an alkoxy group which may be fluorinated, which comprises subjecting a compound having the formula (I):



(I)

wherein A, R^1, R^2, R^3 and R^4 are the same as described above, to oxidation with hydrogen peroxide in the presence of vanadium compounds.

In compounds (I) and (II), the substituents in the ring A include alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio and alkylsulfinyl etc. The alkyl groups are desirably those having 1 to 7 carbon atoms, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl and heptyl etc. The halogen atoms include fluorine, chlorine and bromine atoms, among which the fluorine atom is the most desirable. The carboalkoxy groups are desirably those in which the alkoxy group has 1 to 4 carbon atoms, including carbomethoxy (CH_3OOC-) and carboethoxy (C_2H_5OOC-) etc. The carboalkoxyalkyl groups are desirably those in which the alkoxy and alkyl groups have 1 to 4 carbon atoms each, including carbomethoxymethyl (CH_3OOCCH_2-), carbomethoxyethyl ($CH_3OOCC_2H_4$-), carboethoxymethyl ($C_2H_5OOCCH_2$-) and carboethoxyethyl ($C_2H_5OOCC_2H_4$-) etc. The carbamoylalkyl groups are desirably those in which the alkyl group has 1 to 4 carbon atoms, including carbamoylmethyl (H_2NCOCH_2-) and carbamoylethyl ($H_2NCOC_2H_4$-) etc. The alkoxy groups are desirably those having 1 to 5 carbon atoms, including methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and pentoxy etc. The hydroxyalkyl groups are desirably those in which the alkyl group has 1 to 7 carbon atoms, including hydroxymethyl and 1-hydroxy-propyl-2,1-hydroxyethyl-2,1-hydroxy-2-methyl-propyl-2 etc. The acyl

groups are desirably those having 1 to 4 carbon atoms, including formyl, acetyl, propionyl, butylyl and isobutylyl etc. The acyloxy groups are desirably those in which the acyl group has 1 to 4 carbon atoms, including formyloxy, acetyloxy, propionyloxy, butylyloxy, and isobutylyloxy etc. The aryl groups include phenyl, tolyl and naphthyl etc. The aryloxy groups include phenyloxy, tolyloxy and naphthyloxy etc. The alkylthio groups are desirably those in which the alkyl group has 1 to 4 carbon atoms, including methylthio, ethylthio and propylthio etc. The alkylsulfinyl groups are desirably those having 1 to 6 carbon atoms, including methylsulfinyl, ethylsulfinyl and propylsulfinyl etc.

The ring A is not substituted or is substituted at the 4- or 5-position particularly desirably with alkyl, halogen, trifluoromethyl or alkoxy among the substituents described above.

The N-protective groups represented by R^1 include alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl and alkylsulfonyl etc. The alkyl groups are desirably those having 1 to 5 carbon atoms, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl and pentyl etc. The acyl groups include the same groups as those described for the substituents of the ring A. The carboalkoxy groups include the same groups as those described for the substituents of the ring A. The alkylcarbamoyl groups are represented by the formula:

```
        H
         \
          N-CO-
         /
   alkyl
```

wherein the alkyl group has desirably 1 to 4 carbon atoms, including methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl and isopropylcarbamoyl etc. The dialykylcarbamoyl groups are represented by the formula:

```
   alkyl
        \
         N-CO-
        /
   alkyl
```

wherein the alkyl groups have desirably 1 to 4 carbon atoms each, including dimethylcarbamoyl, diethylcarbamoyl and N-methyl-N-ethylcarbamoyl etc. The alkylcarbonylmethyl groups are represented by the formula: alkyl-CO-CH_2- wherein the alkyl group has desirably 1 to 4 carbon atoms, including acetylmethyl and propionylmethl etc.The alkoxycarbonylmethyl groups are represented by the formula: alkyl-OCO-CH_2- wherein the alkyl group has desirably 1 to 4 carbon atoms, including methoxycarbonylmethyl, ethoxycarbonylmethyl and propoxycarbonylmethyl etc. The alkylsulfonyl groups are represented by the formula: alkyl-SO_2- wherein the alkyl group has desirably 1 to 4 carbon atoms, including methylsulfonyl, ethylsulfonyl, propylsulfonyl and isopropylsulfonyl etc.

The alkyl groups which may be fluorinated, represented by R^2, R^3 and R^4, have desirably 1 to 4 carbon atoms each. Such unsubstituted alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and isobutyl etc. Such fluorinated alkyl groups include trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3,-pentafluoropropyl, 1-(trifluoromethyl)-2,2,2-trifluoroethyl, 2,2,3,3-tetrafluoropropyl and 2,2,3,3,4,4,4-heptafluorobutyl etc.

The alkoxy groups which may be fluorinated, represented by R^2, R^3 and R^4, have desirably 1 to 8 carbon atoms each. Such unsubstituted alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, hexyloxy, heptyloxy and octyloxy. Such fluorinated alkoxy groups include 2,2,2-trifluoroethoxy, 2,2,3,3,3,-pentafluoropropoxy, 1-(trifluoromethyl)-2,2,2-trifluoroethoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,4,4,4-heptafluorobutoxy and 2,2,3,3,4,4,5,5-octafluoropentoxy.

In more detail about the compounds (I) and (II), it is particularly desirable that the ring A is unsubstituted or substituted at the 4- or 5-position with methoxy or trifluoromethyl, R^1 is a hydrogen atom, R^2 and R^4 are

independently hydrogen atom or methyl and R^3 is a fluorinated alkoxy having 2 to 5 carbon atoms.

The vanadium compounds used in this invention include vanadium pentaoxide (V_2O_5), sodium metavanadate ($NaVO_3$), ammonium metavanadate (NH_4VO_3) and vanadium (IV) acetylacetonate [$(CH_3COCH_2COCH_2)_2VO$], desirably vanadium pentaoxide, sodium metavanadate and vanadium acetylacetonate.

The amount of the vanadium compounds used is generally about 0.01 to 10 mole%, desirably about 0.05 to 2 mole%, particularly desirably about 0.1 to 0.5 mole% relative to one mole of the compound (I).

Hydrogen peroxide is usually used in an aqueous solution of hydrogen peroxide, but a solution in an organic solvent such as n-butylalcohol and a solution in the mixture of said organic solvent and water may also be used. The concentration of hydrogen peroxide used in usually 10 to 70%, desirably 20 to 40%, but should not be limited only to these ranges.

The amount of hydrogen peroxide used is usually a slight excess relative to one equivalent of the compound (I), desirably about 1 to 3 equivalents, more desirably about 1 to 1.5 equivalents.

The solvents used for the reaction include halogenated hydrocarbons such as chloroform and dichloromethane, ethers such as tetrahydrofuran and dioxane, alcohols such as ethanol, methanol and isopropanol, ketones such as acetone and methylethylketone, nitriles such as acetonitrile and water, among which ethanol, methanol, acetone and acetonitrile are desirable and ethanol is more desirable. These solvents may be used singly or in combination. The amount of the solvent used for the reaction is about 0.5 to 10 l, desirably about 1 to 5 l, relative to one mole of the compound (I), but should not be limited only to these ranges.

The reaction temperature is usually the temperature under ice-cooling to about the boiling point of the solvents, usually the temperature under ice-cooling to about

40°C, more desirably about 15 to 30°C.

The reaction time is usually about 0.5 to 24 hours, desirably about 1 to 8 hours.

The desired compound (II) produced by the reaction described above is usually separated out as crystals from the reaction mixture, so that the crystals can be collected by filtration after decomposition of the excess of hydrogen peroxide remaining after the reaction by addition of an aqueous solution of sodium thiosulfate, but the crystals may also be collected by extraction with a solvent such as chloroform if necessary, followed by concentration.

The crystals thus collected can be purified if necessary by a routine method such as recrystallization and chromatography.

The starting compounds (I) can be produced by the methods described in, for example, U.S. Patent No.4255431, European Patent Laid-Open No.45200, No.74341, No.80602, No.5129, No.174726, No.175464 and Great Britain Patent Laid-Open No.2134523A, etc.

According to the method for production of this invention, 2-(2-pyridylmethylsulfinyl)benzimidazole can be obtained in a good yield (about 85% or more) and with low production of by-products such as 2-(2-pyridylmethylsulfonyl) benzimidazole N-oxide.

This invention is illustrated in more detail in the following Working Examples and Reference Example.

Example 1

2-[[3-Methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]-methylthio]benzimidazole (monohydrate) (1.77 g) was dissolved in dichloromethane (30 ml), to which was added dropwise at 15-20°C a solution of hydrogen peroxide in t-butanol (2.75 ml corresponding to 0.2 g of hydrogen peroxide) containing vanadium pentaoxide (5 mg), and then allowed to react at 20-25°C for about one hour. After completion of the reaction, an aqueous solution of sodium thiosulfate (0.5 g/30 ml) was added to the reaction mixture, which was stirred vigorously for about 10 minutes, allowed to stand still, and separated into layers. The dichloromethane layer was washed with water (30 ml), and concentrated under reduced pressure; to the residue was

added a mixture of ethanol-water (9:1, 10 ml) for crystallization. This solution was ice-cooled, and the crystals were collected by filtration and washed with an ice-cooled mixture of ethanol-water (8:2). The crystals thus obtained were treated with a mixture of ethanol-water (9:1, 10 ml), heated (65-70°C) and stirred for dissolution of the crystals, then the insoluble matters were removed by hot filtration. The filtrate was ice-cooled for crystallization, and the crystals were collected by filtration, washed with ice-cooled ethanol-water mixture (8:2) and dried in vaccuo to give white crystals of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]methylsulfinyl]benzimidazole (1.64 g). (yield: 93.2%).

m.p. 177-178°C (decomposed)

Example 2

2-[[3-Methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]-methylthio]benzimidazole (monohydrate) (10.0 g) was dissolved in ethanol (75 ml), to which was added a solution of sodium metavanadate (15 mg) in 35% aqueous solution of hydrogen peroxide(3.07 g), and allowed to react by stirring at 20-25° for about 8 hours. After completion of the reaction an aqueous solution of sodium thiosulfate (1 g/5 ml) was added to the reaction mixture, which was stirred vigorously for about 10 minutes. The crystals were collected by filtration and washed with an ice-cooled mixture of ethanol-water (1:1). The crystals thus obtained were treated with a mixture of ethanol-water (9:1, 50 ml), heated (65-70°C) and stirred so that the crystals were dissolved, then the insoluble matters were removed by hot filtration. The filtrate was ice-cooled for crystallization, and the crystals were collected by filtration, washed with ice-cooled ethanol-water mixture (8:2) and dried in vaccuo, to give white needles of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]methylsulfinyl]benzimidazole (9.0 g). (yield: 90.5%).

m.p. 177-178°C (decomposed)

Example 3

2-[[3-Methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]-methylthio]benzimidazole (monohydrate) (20.0 g) was dissolved in ethanol (150 ml), to which was added dropwise at about 20°C a solution of vanadium pentaoxide (30 mg) in a mixture of 35% aqueous solution of hydrogen peroxide (6.14 g) and ethanol (6 ml), and allowed to react at 18-22° for about 2.5 hours. After completion of the reaction an aqueous solution of sodium thiosulfate (2 g/60 ml) was added to the reaction mixture, which was stirred by ice-cooling for about 1 hour. The crystals were collected by filtration and washed with an ice-cooled mixture of ethanol-water (1:1). The crystals thus obtained were treated with a mixture of ethanol-water (9:1, 100 ml), heated (70-80°C) and stirred so that the crystals were dissolved, then the insoluble matters were removed by hot filtration. The filtrate was ice-cooled for crystallization, and the crystals were collected by filtration, washed with ice-cooled ethanol-water mixture (8:2) and dried in vaccuo, to give white needles of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]methylsulfinyl]benzimidazole (17.8 g). (yield: 89.5%).

m.p. 177-178°C (decomposed)

Example 4

Vanadium(IV) acetylacetonate (40 mg) was dissolved in ethanol (150 ml), to which 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]methylthio]benzimidazole (monohydrate) (20.0 g) was added and then 35% aqueous solution of hydrogen peroxide (6.14 g) was added dropwise at 20-25°C, and the mixture was allowed to react at 20-25°C for about 5 hours. After completion of the reaction, a solution of sodium thiosulfate (2.7 g/16 ml) was added to the reaction mixture and stirred vigorously for about 10 minutes. The crystals were collected by filtration and washed with an ice-cooled mixture of ethanol-water (8:2). The crystals thus obtained were treated with a mixture of ethanol-water

(9:1, 90 ml), heated (60-70^{o}C) and stirred so that the crystals were dissolved, then the insoluble matters were removed by hot filtration. The filtrate was ice-cooled for crystallization and the crystals were collected by filtration, washed with ice-cooled ethanol-water mixture (8:2) and dried in vaccuo, to give white needles of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]methylsulfinyl]benzimidazole (18.1 g). (yield: 91.0%).

m.p. 177-178^{o}C (decomposed)

Example 5

Each 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]methylsulfinyl]benzimidazole obtained in Examples 1-4 and in Reference Example described below was analyzed by high performance liquid chromatography (HPLC) and the following results were obtained.

Conditions of HPLC

Equipment used: Shimadzu** High Performance Liquid Chromatograph Type LC-6A

Detector: Shimadzu Ultraviolet Absorption Photometer Type SPD-6A, measurement wave length: 254 nm

Data processor: Shimadzu Type CR-3A

Column: Nucleosil** $5C_{18}$ (150 x 40 mm i.d.)

Column temperature: a fixed temperature of about 25^{o}C

Mobile phase: A mixture of methanol-water-triethylamine (60:40:1) of which pH has been adjusted to 7.0 by addition of phosphoric acid.

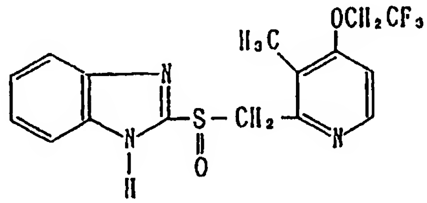
Flow rate: 0.7 ml/min.

Time required for analysis: 30 minutes

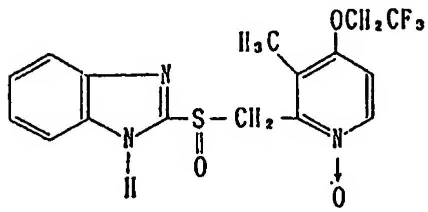
Compound	Area percentage (%) in high performance liquid chromatography				
	Example 1	Example 2	Example 3	Example 4	Reference Example
sulfoxide derivative*1)	99.3	99.6	99.6	99.7	98.9
N-oxide derivative*2)	0.1	<0.1	<0.1	<0.1	0.6

**Trademark

*1)

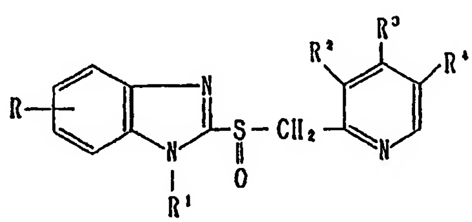


*2)



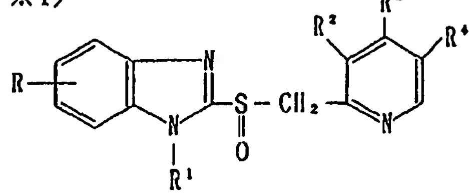
Example 6

According to the same method as in Example 4, the following compounds were produced and analyzed by HPLC under the same conditions as in Example 5; the results are summarized as follows.

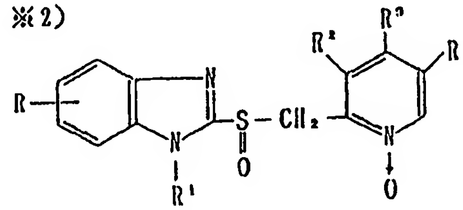


n	R	R^1	R^2	R^3	R^4	m.p. (℃)	yield (%)	Area percentage(%) in HPLC: sulfoxide*1)	N-oxide*2)
1	H	H	CH_3	OCH_2CF_3	CH_3	177～178(d)※	89	99.6	<0.1
1	5−CF_3	H	H	$OCH(CH_3)_2$	H	154～155(d)	87	99.6	<0.1
1	5−CF_3	H	H	OCH_3	H	165～166(d)	88	99.7	<0.1
1	4−CF_3	H	H	OCH_3	H	150～151(d)	86	99.5	0.1
1	5−OCH_3	H	CH_3	OCH_3	CH_3	155～156(d)	87	99.7	<0.1
1	5−CH_3	H	CH_3	OCH_3	CH_3	180～181(d)	88	99.7	<0.1
1	H	CH_2OOCCH_3	CH_3	OCH_3	CH_3	131～133	85	99.6	0.1
1	5−F	H	H	$OCH(CH_3)_2$	H	145～147(d)			
2	5−OCF_3 6−OCF_3	H	CH_3	OCH_3	H	184～185(d)			

※1)



※2)



※)decomposition

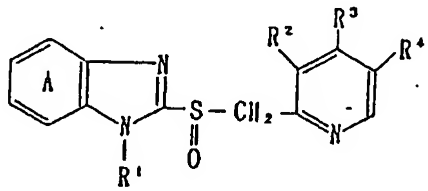
Reference Example

2-[[3-Methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]methylthio]benzimidazole (monohydrate) (20 g) was dissolved in chloroform (200 ml), to which was added slowly dropwise below 5°C a solution of m-chloroperbenzoic acid (13.5 g) in chloroform (200 ml), and stirred at the same temperature for about 10 minutes. After completion of the reaction,the reaction mixture was washed with a solution of sodium hydrogencarbonate, and dried over magnesium sulfate, and chloroform was evaporated off under reduced pressure. To the residue was added ethanol (100 ml) for crystallization, which was ice-cooled; the resulting crystals were collected by filtration and washed with ice-cooled ethanol. The crystals thus obtained were treated with a mixture of ethanol-water (9:1, 90 ml), heated (65-70°C) and stirred so that the crystals were dissolved, then the insoluble matters were removed by hot filtration. The filtrate was ice-cooled for crystallization and the crystals were collected by filtration, washed with ice-cooled ethanol-water mixture (8:2), and dried in vaccuo, to give white needles of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyrid-2-yl]methylsulfinyl]benz-

imidazole (14.9 g, yield: 74.9%).
m.p. 177-178°C (decomposed)

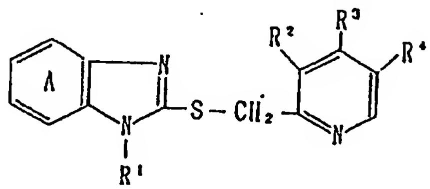
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A method for producing a compound having the formula:



(II)

(wherein the ring A may be substituted; R^1 is a hydrogen atom or an N-protective group; R^2, R^3 and R^4 are independently hydrogen atom, an alkyl group which may be fluorinated or an alkoxy group which may be fluorinated), which comprises subjecting a compound having the formula



(I)

(wherein A, R^1, R^2, R^3 and R^4 are the same as described above), to oxidation with hydrogen peroxide in the presence of a vanadium compound.

2. A method according to claim 1, wherein the substituent of the ring A is C_{1-7} alkyl, halogen, cyano, carboxy, carbo-C_{1-4} alkoxy, carbo-C_{1-4} alkoxy-C_{1-4} alkyl, carbamoyl, carbamoyl-C_{1-4} alkyl, hydroxy, C_{1-5} alkoxy, hydroxy-C_{1-7} alkyl, trifluoromethyl, C_{1-4} acyl, carbamoyloxy, nitro, C_{1-4} acyl-oxy, aryl, aryloxy, C_{1-4} alkyl-thio or C_{1-6} alkyl-sulfinyl.

3. A method according to claim 1, wherein the N-protective group is C_{1-5} alkyl, C_{1-4} acyl, carbo-C_{1-4} alkoxy, carbamoyl, C_{1-4} alkyl-carbamoyl, di-(C_{1-4} alkyl)-carbamoyl, C_{1-4} alkyl-carbonylmethyl, C_{1-4} alkoxy-

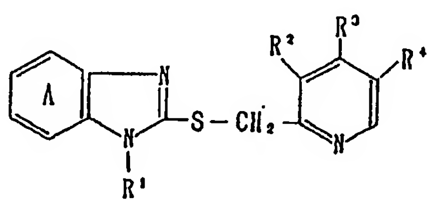
carbonylmethyl or C_{1-4} alkyl-sulfonyl.

4. A method according to claim 1, wherein R^2, R^3 and R^4 are independently C_{1-4} alkyl which may be fluorinated or C_{1-8} alkoxy which may be fluorinated.

5. A method according to claim 1, wherein the ring A is unsubstituted or substituted at the 4- or 5-position with methoxy or trifluoromethyl, R^1 is hydrogen, R^2 and R^4 are independently hydrogen or methyl and R^3 is a fluorinated C_{2-5} alkoxy.

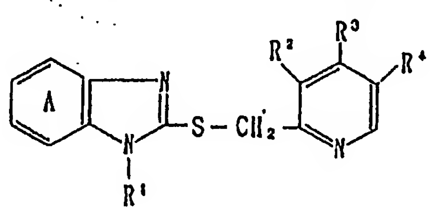
6. A method according to claim 1, wherein the vanadium compound is vanadium pentaoxide, sodium metavanadate, ammonium metavanadate or vanadium (IV) acetylacetonate.

7. A method according to claim 1, wherein the vanadium compound is used in an amount of about 0.01 to 10 mole % relative to the compound having the formula:



(I)

8. A method according to claim 1, wherein hydrogen peroxide is used in an amount of about 1 to 3 equivalents relative to the compound having the formula:



(I)

9. A method according to claim 2 or 3, wherein R^2, R^3 and R^4 are independently C_{1-4} alkyl which may be fluorinated or C_{1-8} alkoxy which may be fluorinated.

10. A method according to claim 2, 3 or 4, wherein the ring A is unsubstituted or substituted at the 4- or 5-position with methoxy or trifluoromethyl, R^1 is hydrogen, R^2 and R^4 are independently hydrogen or methyl and R^3 is a fluorinated C_{2-5} alkoxy.

11. A method according to claim 5, 7 or 8, wherein the vanadium compound is vanadium pentaoxide, sodium metavanadate, ammonium metavanadate or vanadium (IV) acetylacetonate.

12. A method according to claim 2, 3 or 5, wherein the vanadium compound is vanadium pentaoxide, sodium metavanadate, ammonium metavanadate or vanadium (IV) acetylacetonate; the vanadium compound is used in an amount of about 0.01 to 10 mole % relative to the compound of the formula (I); and hydrogen peroxide is used in an amount of about 1 to 3 equivalents relative to the compound of the formula (I).

13. A method according to claim 2, 3 or 5, wherein the vanadium compound is vanadium pentaoxide, sodium metavanadate, ammonium metavanadate or vanadium (IV) acetylacetonate; the vanadium compound is used in an amount of about 0.05 to 2 mole % relative to the compound of the formula (I); hydrogen peroxide is used in an amount of about 1 to 3 equivalents relative to the compound of the formula (I) using a solvent selected from the class consisting of halogenated hydrocarbon solvents, ether solvents,

alcohol solvents, ketone solvents, nitrile solvents, water and mixtures thereof; and the oxidation reaction is carried out at an ice-cooling temperature to about 40°C.

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